

Antagonism Among Diseases

The question of antagonism among diseases has intrigued physicians, especially those philosophically inclined, for centuries. Opinions on the subject have been based largely on clinical or epidemiologic impression, and relatively rarely on statistically controlled observation.

The evidence for an antagonistic effect of one disease upon another has rested largely on judgments on the prevalence of two diseases in a given locality. At one time, for example, it was believed that a "mutual exclusiveness" existed between typhoid fever and malaria. Persons long resident in malarious regions were believed to have lost an originally natural susceptibility to typhoid fever (²). The original, and certainly quite uncontrolled observations leading to this concept, were made in Algiers and Italy. Hirsch cited many

later reports from other countries, including the United States, supporting the hypothesis of such an antagonism.

Most of such concepts have been abandoned in the light of later study. Indeed, as far as typhoid fever and malaria were concerned, physicians in the United States, at the time of the Civil War, believed loosely in the existence of a combination of the two diseases. All this was before the advent of specific concepts of the etiology of the two diseases based on later knowledge from bacteriology and parasitology.

Yet in more recent times other antagonisms among microbial diseases, resting on a more readily established foundation, have been recognized, e.g., that between malaria and the dementia paralytica of cerebral syphilis. However, in this case,

the concept has not been of one micro-organism pitted against another, but rather of a quite nonspecific effect, viz., of the fever of malaria upon the growth capacity of the treponoma invading the brain. The therapy of induced malaria for the syphilitic state gave way in many hands to the treatment of dementia paralytica by artificial fever. It is interesting to recall that in leprosy also the possible ameliorating effect of artificial hyperthermia has been explored. In each of these cases, it is perhaps needless to say, the artificial hyperthermia to prevent microbial proliferation was abandoned with the advent of a more successful antimicrobial chemotherapy.

Yet the fact that one microbe may have a restraining effect upon another is incontestable. The effect of contaminants in bacterial cultures is a daily experience of bacteriologists, and the therapeutic action of penicillin, a product of a mold, *Penicillium notatum*, on a wide variety of bacteria, is also a daily observation. Incidentally, the opposite sort of effect, the restraining influence of the normal predominant flora of the bowel on the proliferation of molds, is also well known; witness the devastating mold-induced colitis that sometimes occurs when the normal flora of the bowel has been largely wiped out by antibiotics to which molds are not susceptible.

Recent numbers of the INTERNATIONAL JOURNAL OF LEPROSY have raised the question of microbial antagonisms toward leprosy. In the Current Literature section of this issue of THE JOURNAL (pp. 337-338) there is an abstract of an article by a veteran in the field, and long-time Associate Editor of THE JOURNAL, R. Chaussinand, in which the question of antagonism between leprosy and tuberculosis is raised. Chaussinand stressed the apparent fact that in a number of countries, e.g., Portugal, the prevalence of autochthonous leprosy, was in general inversely proportional to the mortality rate from pulmonary tuberculosis. Chaussinand freely admitted that the apparent mutual exclusiveness was not necessarily or even primarily an immunologic matter, but rather a much more complex affair, in which social as well as biologic factors were vitally concerned. Indeed, it would

be difficult to sustain the concept of a specific immunologic exclusiveness of the two diseases in view of the high mortality of leprosy patients from pulmonary tuberculosis, although it is to be noted, in this relation, that the high mortality has been observed principally among patients with leprosy of lepromatous type, among whom reactive power to bacterial infection in general may be much reduced. It is not out of context to note the rising trend in the use of an artificial tuberculosis, viz., BCG vaccination, in the prevention of leprosy. Present results ⁽¹⁾ indicate that it is particularly efficacious against the tuberculoid form of leprosy. It is reasonable to believe that in this case specific immunologic factors are concerned.

Of at least equal interest, although still less controlled statistically, are numerous reports on the validity of a possible mutual exclusiveness between leprosy and cancer. In a preceding number of THE JOURNAL a study by Keil ⁽⁵⁾ on the relation between carcinoma and leprosy was noted in abstract. Keil came to the conclusion that the relative cellular and tissue reactivities of lepromatous and tuberculoid leprosy patients were such as to make the spread of carcinoma, in the advent of cancer invasion, much more likely in the former than the latter type. An actual review of the findings of some 17 authors appeared to Keil to substantiate this theoretic concept. His review of their studies brought out the fact that carcinomatous development was twice as frequent in lepromatous as in tuberculoid cases.

In the current issue of THE JOURNAL at least three items bear on the relations and possible mutual exclusiveness of carcinoma and leprosy. Two original articles illustrate a common finding, viz., that early reports of an antagonism or mutual exclusiveness do not hold up in the light of thorough, controlled study. Michalany ⁽⁷⁾ noted that up to about twenty years ago the impression prevailed that leprosy and cancer were rarely associated in the same patient. Many records in the literature seemed to sustain this opinion. Studies in 1937 by two Brazilian authors ⁽⁶⁾, however, made on a larger series of

cases than were considered in most of the studies in the past, indicated that cancer was not rare in leprosy patients, and that there was no reason to believe in an incompatibility of the two diseases. Michalany's own studies, based on observation of 539 cases of malignant tumors of the skin in patients with leprosy, have strongly supported this view.

In another original article in this issue of *THE JOURNAL* Riedel has revised a previous concept of his own in this respect. Job and Riedel had stated that "Carcinoma arising out of plantar ulcers seems to be extremely uncommon." Riedel's later studies have led him to the conclusion that malignancy in plantar ulceration in leprosy is not quite as rare as is generally believed, and that it may develop sooner than is likely to be expected.

Such studies inevitably tend to our own conclusion that more extended studies generally lead to revision of early notions based on inadequate data. So many biologic factors, including age and varying degrees of exposure to environmental influences, come into play, that large volumes of data and careful statistical evaluation are necessary to establish what we ultimately may accept as facts. But the very volume of past conflicting data overwhelms us. The association of cancer and tuberculosis has been a similar problem, with proponents for and against a mutually exclusive relation. Everybody knows that the two diseases may occur in the same body, but the frequency of such association in the light of statistical controls, taking account of varying environmental factors, and the fact that one disease, tuberculosis, is declining in prevalence, while the other, cancer, is rising, is still a subject of controversy.

Finally a query has been made in this issue of *THE JOURNAL* ⁽⁹⁾ with regard to the association of malignant lymphomas and leprosy. Substantial information on the subject being as slender as it is, it will not be surprising if a long time is required to reach a satisfactory conclusion relative to the frequency of this association. The problem is complicated by the inadequacy of data on the etiology of the two diseases.

Leprosy is presumptively of bacterial origin; some, at least, of the lymphomas appear to be of viral etiology. The field of virus research is expanding so rapidly that elements that may be of importance develop frequently and unexpectedly. For example, the discovery of "interferons" by Isaacs and Lindenman ⁽³⁾ in the laboratories of the National Institute for Medical Research in London, now accepted and well studied as elements concerned in resistance to and recovery from virus infections, may be pertinent in connection with the problems of viral tumors. Studies on these unique substances have shown that the products of damage to a cell by one virus may have an inhibiting effect on the proliferation of another virus. It is too early to say, but it is fair to state now that the problem is highly complex, and far from easily solved.

In general, studies in the field of antagonism between leprosy and other diseases, are much too fragmentary to settle most of the major questions at issue. But there is little doubt that adequate investigation with proper statistical control of all variables presently recognized, would be rewarding for understanding of the natural history of leprosy.

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